PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity score matched cohort study and a meta-analysis
AUTHORS	Yousufuddin, Mohammed; Takahashi, Paul Y.; Major, Brittny; Ahmmad, Eimad; Al-Zubi, Hossam; Peters, Jessica; Doyle, Taylor; Jensen, Kelsey; Al Ward, Ruaa; Sharma, Umesh; Seshadri, Ashok; Wang, Zhen; Simha, Vinaya; Murad, M. Hassan

VERSION 1 – REVIEW

REVIEWER	Hedley Knejwen Quintana Department of Research and Health Technology Assessment Gorgas Memorial Institute for Health Studies Panama City, Panama
REVIEW RETURNED	15-Mar-2019

GENERAL COMMENTS	First of all, I consider that you did a great job writing the manuscript and I hope it be published soon! However; I need to understand some issues: 1- As far I understood, the authors state that mortality sources are solely obtained from local Health Systems. I wonder whether are there other sources of registered deaths besides the ones the authors described, for example are death due murders, suicides, misadventures registered as among your data? In my view, they hold capital importance! if they cannot be included, it is a limitation of study. 2-As far I read the manuscript, I have not found information regarding laboratory data during admision that might change the prognosis of the patients and perhaps also their lipid profile. For example, kidney function, electrolytes, liver function etc. Can the authors provide such data? if not, could the authors explain why they were not capable to get such data? The same could be said about medication, physical activity, as well as, diet. If 3-Regarding the meta-analysis, have you found a paper we wrote regarding this topic when I was studying my PhD studies? If they have found it, could they explain why did they exclude it? If they have not found it, explain why it was not originally found, and how the authors search strategy changed and how such change the results of the meta-analysis. 4-Can the author show the STROBE and MOOSE checklists regarding this manscript? BMJ Open requires that the authors present these checklists. Despite the journal requirements, in my

	view such checklists greatly improves the quality of the paper and any missed item of both checklist must be added to the manuscript and reported in the checklist. The MOOSE checklist guides the authors to properly answer queries under comment 3. 5-This is minor comment regarding statistics: when someone works with cohorts or RCTs, the intercept of each model is not required to be reported. However; such element of model is required for predicting future events, for example, some known scores such as the Framingham need it. Can the author present the intercept of the models? if they cannot, please explain why. 6-Do the authors have information regarding ejection fraction (EF) of the patients? If they do, is it possible to do sensitivity analyses regarding those with and without normal EF?

REVIEWER	Martin Frydland Department of Cardiology Hvidovre Hospital Copenhagen, Denmark
REVIEW RETURNED	05-Apr-2019

GENERAL COMMENTS	Hyperlipidaemia is associated with lower mortality after incident acute myocardial infarction or acute decompensated heart failure: A propensity matched cohort study and a meta-analysis The manuscript presented by Dr. Yousufuddin and colleagues assessed patients with the diagnosis of hyperlipidaemia and/or high LDL-C vs. patients without and myocardial infarction or heart failure. The paper is well written although I have some concerns. Major concerns 1. The subject may be of limited clinical relevance, as patients with hypolipidemia often are old and frail. As the authors find an association between this and mortality is not surprising. This should be discussed more thoroughly. 2. I think looking at both heart failure and ACS in the same paper is somewhat confusing. Consider looking at AMI and dividing patients into NSTEMI/STEMI solely and HF in another manuscript. 3. When looking at the cumulative incidence of patients with AMI, you get the impression, that the curves separate immediately after the incident. This should be discussed. AMI patients dying within the first 30 days, dies from cardiovascular causes (cardiogenic shock etc). Statistical concerns 1. The analyses on the propensity score matched cohort should be done with care. For this to make sense the model should be able to predict HLP/non-HLP in the logistic regression model. Therefore, the C-statistics for the model should be presented. 2. The authors should present the model control for the cox proportional hazard model

REVIEWER	Uffe Ravnskov Independent researcher Lund, Sweden
REVIEW RETURNED	24-May-2019

GENERAL COMMENTS	High LDL- cholesterol may be beneficial
	The interesting and well-constructed study by Yusuffudin et al. is a strong support of the view that high LDL-cholesterol (LDL-C) may be of benefit; in particular because some of the studies, which they consider as contradictive, are in fact supportive. In the start they mention that LaRosa et al. (ref. 1) and Yusuf et al. (ref. 2) support the general view about cholesterol. However, in the review by LaRosa et al. at least five studies with contradictory result were ignored, and two contradictory studies were mentioned as if they were supportive.[1] In the study by Yusuf et al. no information was given about total or LDL-cholesterol as risk factors; they have only discussed the associations with the less accurate apoB/apoA1 ratio. Yusuffudin et al. also mention that lipid lowering by statin treatment decreases the risk of incident AMI and cardiovascular mortality and refer to the CCT meta-analysis (ref. 3) and the meta-analysis by Silverman et al. (ref. 4). It is questionable that these papers prove that statin treatment is beneficial because according to figure 5 in the CCT meta-analysis, the absolute risk reduction of total mortality per 1 mmol/l reduction of LDL-cholesterol was only 0.2 % per year, and for CHD mortality it was only 0.1% per year. In the meta-analysis by Silverman et al., the authors have ignored or excluded nine trials with minimal benefit or with no benefit at all.[2] In four of them[3-6] total mortality had increased in the treatment group; in two of them[3,4] even CHD mortality had increased. Furthermore, in four statin trials, where a high-degree lowering of LDL-C was compared with a low-degree lowering, no significant difference with respect to the number of major vascular events was obtained, although LDL-C was lowered by 0.4–1 mmol/L more in the high-dose groups.[7-10] The study by Velagaleti et al. (ref. 6) is mentioned as supporting an association between hyperlipidaemia and heart failure. However, no association was found in the long-term follow-up between non-HDL and heart failure after correction for myocardial infarctions (table 3). The positive association in the shorter follow-up may have been obtained because the authors have analysed non-HDL only. Yusuffudin et al. mention that the studies by Granger et al. (ref.10) and Krumholz et al. (ref.11) support the general view as well.

	However, according to table 2 in the study by Granger et al., mortality among those with hyperlipidaemia was 2.8% and among those without hyperlipidaemia it was 5.8% ($p<0.001$). In the study by Krumholz et al., the risk factor-adjusted odds ratio for all-cause mortality was 0.99 for the group who had cholesterol levels greater than or equal to 6.20 mmol/L (≥240 mg/dL), and 1.00 for the group who had levels less than 5.20 mmol/L (<200 mg/dL). The study by Al-Mallah et al.[11] should be mentioned as well. They found that LDL-C of patients with acute myocardial infarction (AMI) at the time of admission to hospital was lower than normal. They decided therefore to lower the patients' LDL-C even more, but at follow-up three years later, total mortality among those with LDL-C below 105 mg/dl (2 mmol/l) was twice as high compared to those with a higher LDL-C, even after adjustment for confounding variables (14.8% vs. 7.1%, $p = 0.005$). Supporters of the general view may argue that familial hypercholesterolemia (FH) has shown that high LDL-C is an important risk factor. However, there is much evidence that the cause of early AMI in FH individuals is not their high LDL-C but increased coagulation factors, which a few of them have inherited as well.[12] Taking all findings together, there is strong support for the view that high LDL-C is beneficial. Statin treatment may be able to lower the risk of non-fatal cardiovascular events a little, but considering that many events may heal with few sequels or none at all, and that the number of serious side effects is much higher than reported in the statin trials,[2,13,14] a relevant question is, if this type of prevention is reasonable, in particular for healthy people. There is a number of minor linguistic errors in the text, but as English is not my mother tongue I suggest that the authors themselves re-read the text carefully. **References** 1. Ravnskov U. Quotation bias in reviews of the diet-heart idea. *J Clin Epidemiol* 1995;48:713–9.

2. Ravnskov U, de Lorgeril M, Diamond DM et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. *Exp Rev Clin Pharmacol* 2018;11:959-70. doi: 10.1080/17512433.2018.1519391.
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12. Ravnskov U, de Lorgeril M, Kendrick M, Diamond DM. Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia. *Med Hypotheses* 2018;121:60-3. doi: 10.1016/j.mehy.2018.09.019.
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VERSION 1 – AUTHOR RESPONSE

Following are the brief responses to editorial and reviewers' comments. Detailed response was attached as a separate file

Response to editorial comments (Responses highlighted in yellow in the text)
1. Title revised to non-declarative form
2. Strengths and limitations are revised according to suggestions
3. The author contribution statement was revised and incorporated in the footnotes
4. PRISMA check list is completed and included in the supplement material
5. Methods for systematic review and meta-analysis are elaborated with 2 additional paragraphs are added and highlighted in yellow
6. STROBE check list is completed and included in the supplement material
7. Hyperlipidemia is clearly defined in the abstract

Response to Reviewer # 1 comments (Responses highlighted in blue in the text)
1. Details of mortality data acquisition, updates, and entry in to electronic medical records at Mayo Clinic are described.
2. Relevant new laboratory data on LDL-C, sodium level, BUN, and creatinine were collected from electronic medical records. A series of new sensitivity analyses were performed among patient with these data points available. Methods, results, and discussion sections are updated and highlighted in blue. A new table summarizing these findings was created and incorporated in the manuscript. New figures related to new Kaplan-Meier estimates related to association between LDL-C quartiles and time to death were incorporated in Figure 1.
3. We searched all relevant data bases and did not find the manuscript co-authored by the reviewer.
4. STROBE check list is completed and included in the supplement material
5. Replied to the reviewer about not using intercept for each model in our meta-analysis.
6. We extracted new data on LVEF. New sensitivity analyses are performed among patient with data available on LVEF. Methods, results, and discussion sections are updated and highlighted in blue. A new table summarizing this new finding is created and incorporated in the manuscript.

Response to Reviewer # 2 comments (Responses highlighted in green in the text)
1. Separate analysis was performed in persons <65 years and those ≥ 65 years and no differences were found. Frailty indicators could not be obtained. Instead, we use BMI as a covariate and performed sensitivity analysis. These are described in methods, results, and discussion section.
2. Rationale for inclusion of both AMI and HF cohorts in one paper is explained.
3. Explanation for early separation of Kaplan-Meier curves in patients with or without hyperlipidemia in both AMI and HF cohorts is described in results section and discussed in discussion section.
4. Reasoning for not using c-statistics is discussed.
5. Clarification for not using the model control for the cox proportional hazard model is provided

Response to Reviewer # 3 comments (Responses highlighted in pink in the text)

1. We rephrased the sentences and deleted the references by LaRosa et al and Yusuf et al.
2. We provided our justification for not going into statin trial in detail, since it is not the focus of current study
3. We offered our reasoning for appropriate citing of the report by Velagaleti et al.
4. We revised and appropriately cited Granger et al and Krumholz et al studies in the text.
5. We discussed the findings of the report by Al-Mallah et al, and cited in our discussion section
6. We broadly discussed genetic studies and cited the article by Ravnskov et al. Med Hypotheses. 2018;121:60-3
7. Given study limitations, we are cautious in making declarative statements.
8. Revise for English language and topographical errors

VERSION 2 – REVIEW

REVIEWER	Hedley Quintana Gorgas Memorial Institute for Health Studies
REVIEW RETURNED	15-Oct-2019

GENERAL COMMENTS	When I respond to the reviewers, I thank the authors if they can cite the reviewer's comment they refute. Please, do the same. Again, I think this exchange of ideas will make the manuscript clearer for each of the reviewers and for the authors! "Response to Reviewer # 1 comments (Responses highlighted in blue in the text) 1. Details of mortality data acquisition, updates, and entry in to electronic medical records at Mayo Clinic are described." -Such information is needed to better understand the outcome. USA death certification is not uniform and it might change from county to county. An international reader better understands how where such information comes from. I thank the authors for providing such information. "2. Relevant new laboratory data on LDL-C, sodium level, BUN, and creatinine were collected from electronic medical records. A series of new sensitivity analyses were performed among patient with these data points available. Methods, results, and discussion sections are updated and highlighted in blue. A new table summarizing these findings was created and incorporated in the manuscript. New figures related to new Kaplan-Meier estimates related to association between LDL-C quartiles and time to death were incorporated in Figure 1." -Agree, such information really helps the reader to better understand possible confounders and effect modification variables "3. We searched all relevant data bases and did not find the manuscript co-authored by the reviewer." -Such paper is not found in relevant data bases. I don't expect if solves the research question. If you want to read it, this is the link for the article: https://www.sciencedirect.com/science/article/pii/S2214762416300159 "4. STROBE check list is completed and included in the supplement material" - I see the STROBE checklist. However, you also added the PRISMA checklist. You've had should written it down in you your response to the reviewer. "5. Replied to the reviewer about not using intercept for each model in our meta-analysis." - Could you tell me when did the author explain about the intercept use? For Cox models, the intercept seems meaningless. "6. We extracted new data on LVEF. New sensitivity analyses are performed among patient with data available on LVEF. Methods, results, and discussion sections are updated and highlighted in blue. A new table summarizing this new finding is created and incorporated in the manuscript." -Very good!

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 comments:

Comment #1: Details of mortality data acquisition, updates, and entry in to electronic medical records at Mayo Clinic are described."

-Such information is needed to better understand the outcome. USA death certification is not uniform and it might change from county to county. An international reader better understands how where such information comes from. I thank the authors for providing such information.

Authors' response: We greatly appreciate positive remarks by the reviewer

Comment #2: Relevant new laboratory data on LDL-C, sodium level, BUN, and creatinine were collected from electronic medical records. A series of new sensitivity analyses were performed among patient with these data points available. Methods, results, and discussion sections are updated and highlighted in blue. A new table summarizing these findings was created and incorporated in the manuscript. New figures related to new Kaplan-Meier estimates related to association between LDL-C quartiles and time to death was incorporated in Figure 1."

-Agree, such information really helps the reader to better understand possible confounders

and effect modification variables

Authors' response: We greatly appreciate positive remarks by the reviewer

Comment #3: We searched all relevant data bases and did not find the manuscript co-authored by the reviewer."

-Such paper is not found in relevant data bases. I don't expect if solves the research question. If you want to read it, this is the link for the article:

https://www.sciencedirect.com/science/article/pii/S2214762416300159

Authors' response: We are very humbled and highly appreciate of the Reviewer #1 and providing the link for very relevant article related to our manuscript which we unfortunately missed in our search. We read this article with great enthusiasm. We cited this study in our manuscript and incorporated a portion of the results of this important study in our meta-analysis and represented it in supplemental table. We revised our meta-analysis results and recalculated the effect size.

This was highlighted in green

Comment #4: STROBE check list is completed and included in the supplement material"

- I see the STROBE checklist. However, you also added the PRISMA checklist. You've had should written it down in you your response to the reviewer.

Authors' response: We appreciate the reviewer's remarks. We addedd STROBE check list as per the reviwer's suggestion and PRISMA check list in accordance with editorial recommendation. We apologise for not carifying these suggestions in our earlier response to reviewers.

Comment #5: Replied to the reviewer about not using intercept for each model in our meta-analysis."

- Could you tell me when did the author explain about the intercept use? For Cox models, the intercept seems meaningless

Authors' response: We appreciate the reviewer's remarks. We pooled the effect sizes (in this case, hazard ratio) reported by the studies. We didn't pool the intercept of the models as most were not reported. Additionally, the methods to generate the pooled intercept are not well developed either.

Comment #6: We extracted new data on LVEF. New sensitivity analyses are performed among patient with data available on LVEF. Methods, results, and discussion sections are updated and highlighted in blue. A new table summarizing this new finding is created and incorporated in the manuscript."

-Very good!

Authors' response: We greatly value the reviewer's positive comment